Synthesis of an extended structure porphyrin lanthanide complex for use as a near infra-red imaging agent

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Abstract

This paper reports the synthesis and thermal Bergman cyclization of 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin to generate the chromophoric superstructures bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin and 2,3-diethynyl-5,20-diphenyl-piceno[10,11,12,13,14,15-fghij]porphyrin. Problems concerning the cyclization and new routes to our desired compound are discussed within. These chromophores, when paired with a near-IR emitting metal center, have potential as *in vivo* imaging agents.

Introduction

In order for a molecule to work as an effective near infra-red imaging agent *in vivo*, it must absorb light in the red region of the electromagnetic spectrum, and emit light in the near infra-red region. These types of molecules are potentially useful in biological systems because human tissue is largely transparent to both red and near infra-red wavelengths. For an effective imaging agent to be designed, the molecule requires two parts: a chromophore and an emissive band in the desired spectral region with a high quantum yield. If this molecule is to be delivered into a human system, light would be directed through the skin and absorbed by the chromophore. In the system we are designing, this absorbed energy is then passed into the metal center of the molecule. This metal center would then emit light in the near IR region, where it can be detected by an imaging system.

To best fulfill this requirement, a member of the lanthanide series will serve as our metal center. Their optical properties, such as line-like emission spectra and long luminescence lifetimes have been studied.[1] These properties make this series of

elements likely candidates as fluorescence imaging agents. Some lanthanides, like Eu (III) and Tb (III) possess strongly emissive and long-lived excited states, but do not exhibit intense absorption bands.[2] This means that these ions require a chromophore to harvest the energy and transfer it to the emitting metal center. Several of the lanthanide (III) ions are luminescent in the near-IR region,[3] while porphyrins have strong absorption bands in the visible region.[4] If these two components were to be paired together, the resulting molecules would be ideal candidates for efficient photo-sensitizers and luminescence imaging agents. The quantum yield of the overall process, which involves the excitation of the chromophore and intersystem crossing to the triplet state; energy transfer to the lanthanide ion; and the resultant lanthanide emission, depends on the efficiency of the individual steps (Figure 1).[5] Quantum yield is

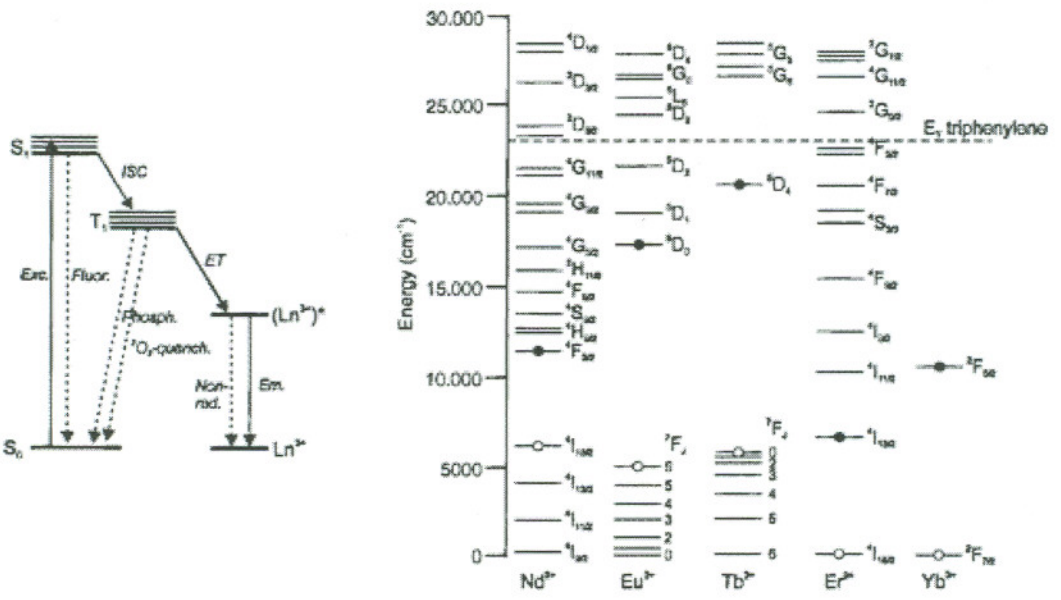


Figure 1. Left: Photophysical model describing the main pathways in the sensitization process. Right: Energy diagram of the 4f levels responsible for the lanthanide luminescence, where a filled circle denotes the lowest luminescent state and an open circle denotes the highest nonluminescent state. [5]

defined as the factor of photons absorbed by photons emitted. It is important that quantum yields be high for imaging compounds because the higher the quantum yield, the easier it is to measure the emission. Recent literature has reported that lanthanides have low quantum yields, generally less than 0.3.[5-11] This problem is one that will be addressed by our ensuing research, possibly by the use of lanthanide clusters. Research on the metal center aspect of this project will be included in future work.

Work so far on this project has involved synthesis of the chromophore. Molecules that are good chromophores generally have extended conjugated structures that allow for high delocalization of the π system. The structure we chose for the core of our chromophore was 5,10,15,20-tetraphenylporphyrin. This purple solid has been widely studied, and has a facile, known synthesis.[12] Through a number of synthetic steps we have added two enediyne units at the β positions to this porphyrinic core, making 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin. We then attempted to create an extended conjugated structure using Bergman cyclization. This process rearranges a Z-1,5-diyne-3-ene unit to a 1,4-didehydrobenzene diradical. In the presence of a hydrogen source, this diradical can be quenched to afford the benzannulated product.[13] (Figure 2). Described here is the synthesis and attempted

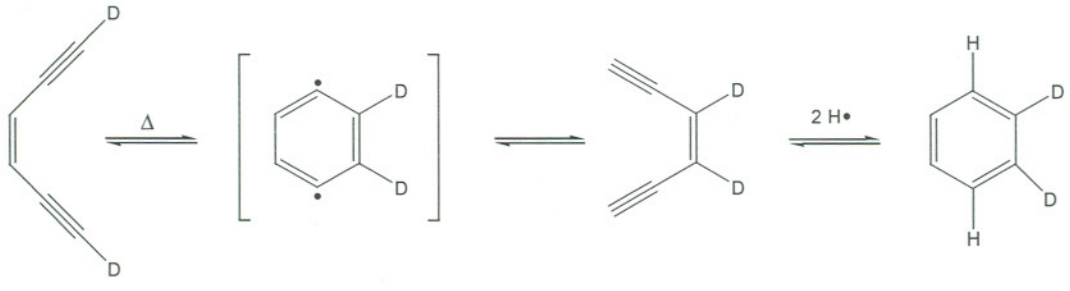
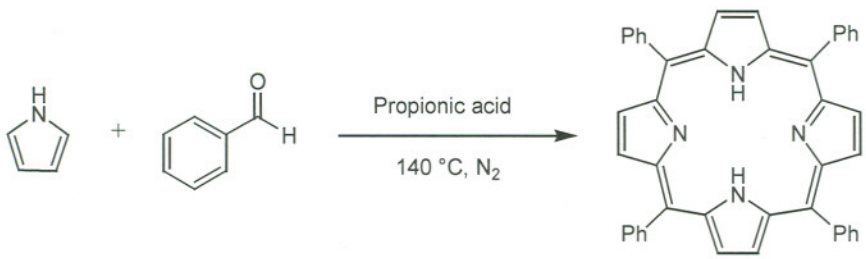


Figure 2. Bergman cyclization equilibrium of the 1,5-diyne-3-ene unit and trapping of the *p*-benzyne diradical intermediate. [13]

thermal cyclization of free base and Zn (II) 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin.

Results and discussion

A series of new compounds were prepared by using 5,10,15,20-tetraphenylporphyrin **1** (TPP) as a starting material. The TPP was prepared by following the known literature procedure (Scheme 1).[12] The first molecule synthesized was 2,3,12,13-tetrabromo-5,10,15,20-tetraphenylporphyrin (**2**). This was prepared by refluxing five equivalents of N-bromosuccinimide (NBS) with TPP in $CHCl_3$ for 24 hours (Scheme 2). Electrophilic bromination occurs regiospecifically at the antipodal pyrrole ring of free-base porphyrins that have substituents which fix the aromatic delocalization pathway.[14] This occurs quite readily, and affords **2** in high yield (80%).



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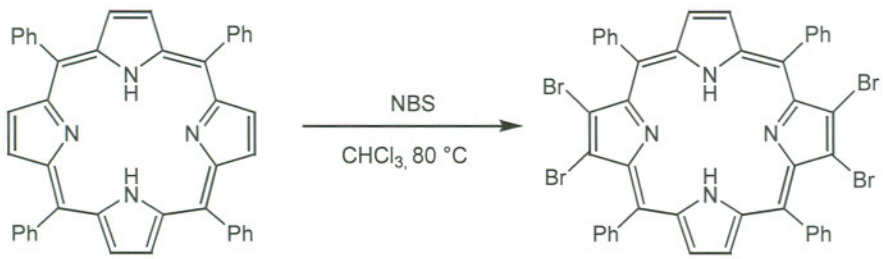
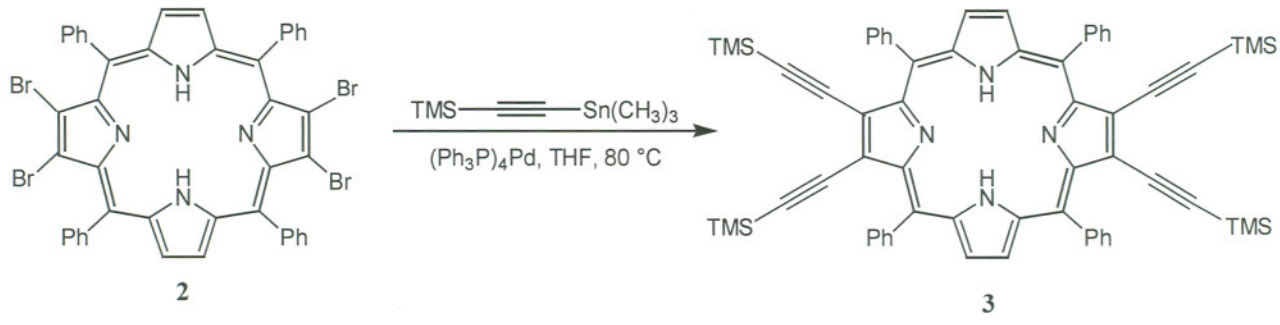
Scheme 1. Synthesis of 5,10,15,20-tetraphenylporphyrin (**1**).



1 **2**

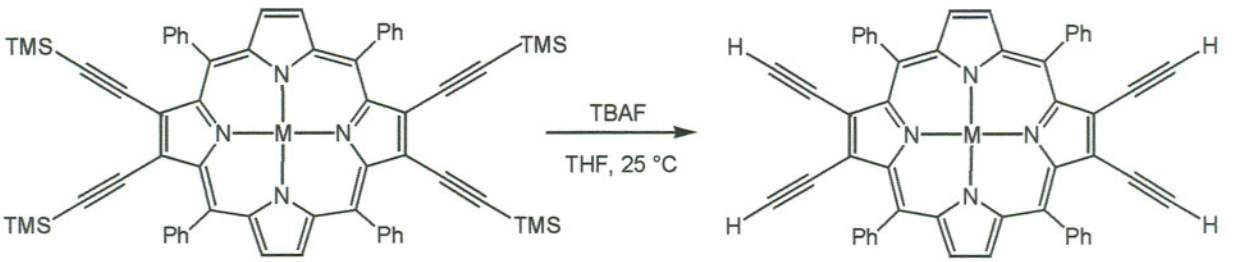
Scheme 2. Synthesis of 2,3,12,13-tetrabromo-5,10,15,20-tetraphenylporphyrin (**2**).

In order to prepare the molecule for Bergman cyclization, we had to replace the bromines at the 2,3,12,13 positions with ethynyl units. This was accomplished by treating **2** with six equivalents of trimethyl(trimethylstannanylethynyl)silane (TMS–≡–$Sn(CH_3)_3$) over a Pd^0 catalyst in an inert atmosphere (Scheme 3). Addition of the trimethylsilylethynyl units was a facile reaction, and afforded 2,3,12,13-tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin **3** in high yield (75%).



Scheme 3. Synthesis of 2,3,12,13-tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin (**3**).

Zinc was inserted into 2,3,12,13-tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin (**3**) by stirring it with zinc acetate for one hour in $CHCl_3$/MeOH. Free base and zinc (II) 2,3,12,13-tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin were deprotected at room temperature with five equivalents of tetra-butyl ammonium fluoride (TBAF) in THF and afforded the corresponding tetraethynyl products **4** and **8** in high yields (90%) (Scheme 4).



3, M = 2H
7, M = Zn

4, M = 2H
8, M = Zn

Scheme 4. Synthesis of 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin (**4**) and zinc (II) 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin (**8**).

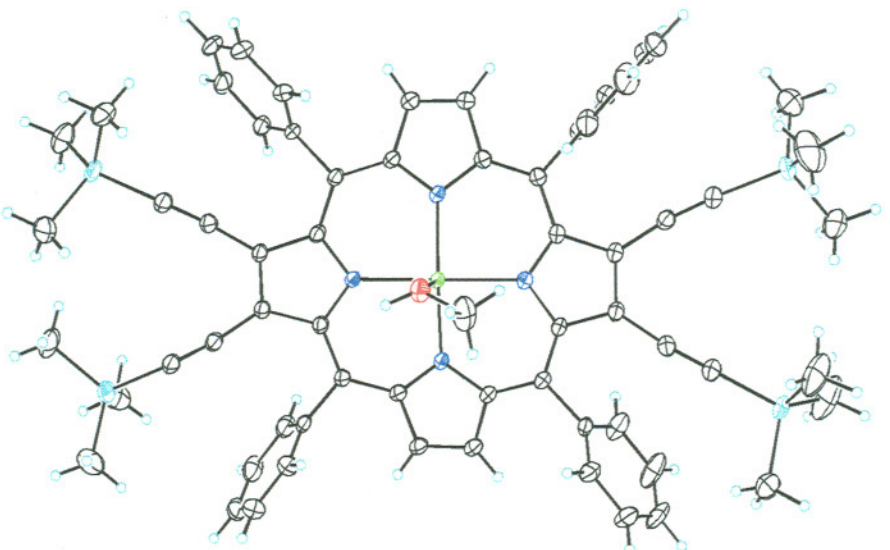
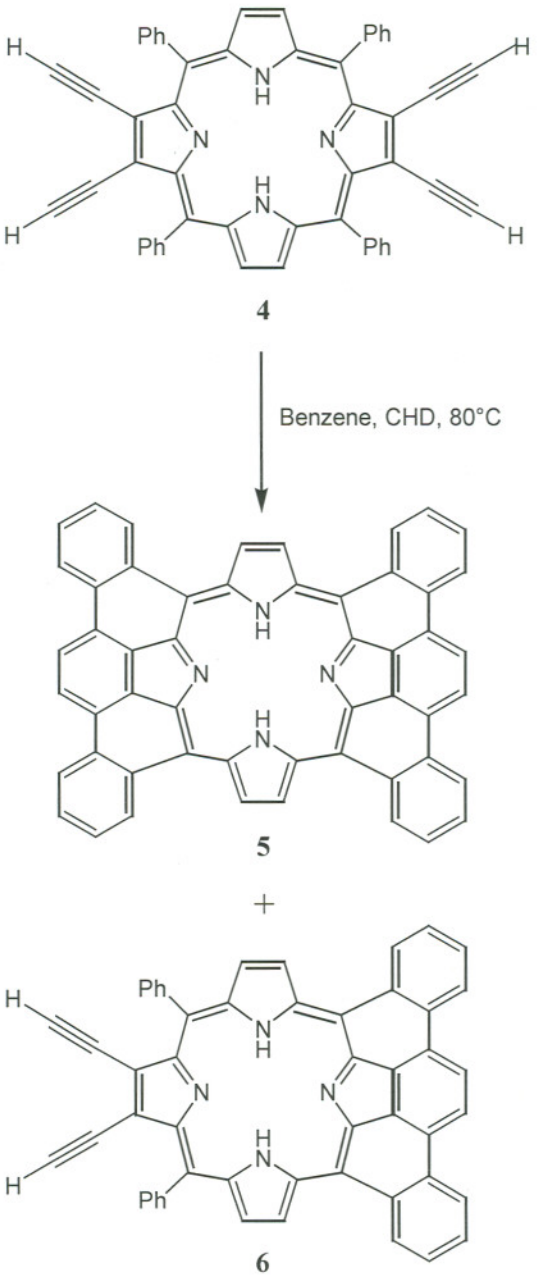


Figure 3. X-ray structure of **7**.

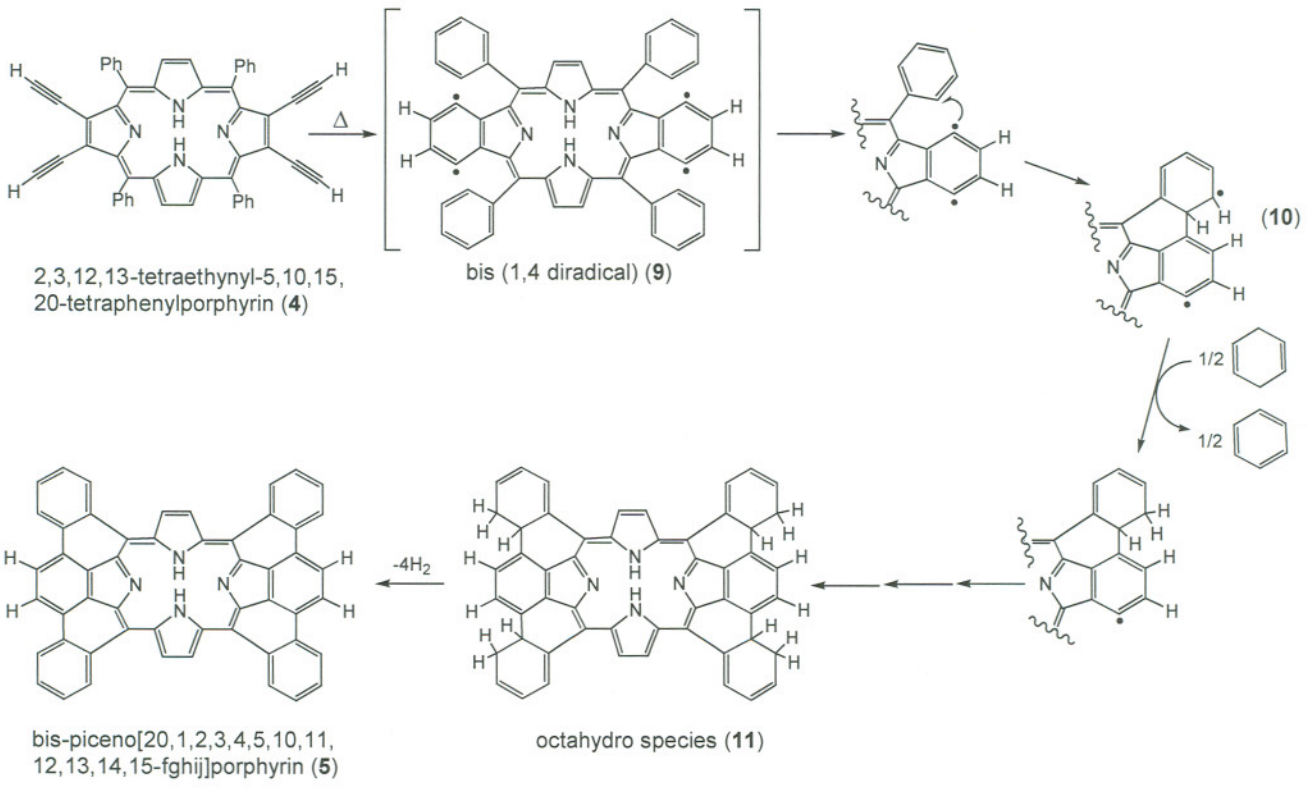


Scheme 5. Synthesis of bispiceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin (**5**) and 2,3-diethynyl-5,20-diphenylpiceno[10,11,12,13,14,15-fghij]porphyrin (**6**).

Thermal Bergman cyclization of **4** afforded a mixture of bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin **5** and 2,3-diethynyl-5,20-diphenylpiceno[10,11,12,13,14,15-fghij]porphyrin **6** (Scheme 5). Cyclization was carried out in benzene at 80 °C by using 1,4-cyclohexadiene (CHD) as a hydrogen

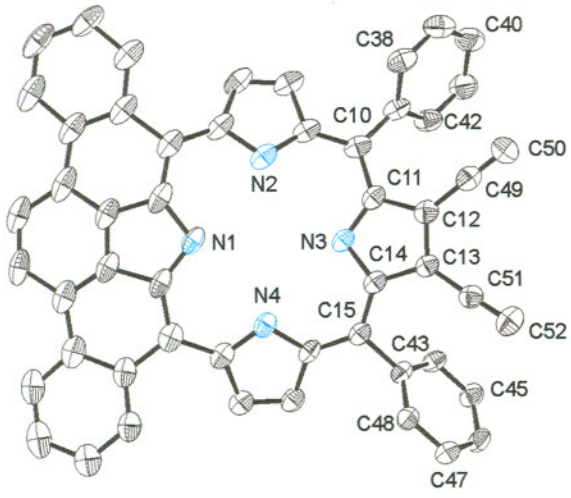
source. This reaction has proved to be challenging, due to the radical nature of the intermediate. The proposed mechanism for cyclization, adapted from Aihara *et al* [15], is shown in Scheme 6. Thermal Bergman cyclization of the alkynyl moieties generates a bis(1,4-diradical) species **9**. This diradical is then transferred to the adjacent *meso*-phenyl groups, which spawns a planar diradical species **10**. This radical is quenched by four successive hydrogen transfers from CHD, to afford the octahydro species **11**. This is then oxidized upon work up to give bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin **5**. Polymeric and oligiomeric compounds have been known to form from this type of reaction.[16] Indeed, polymerization has been an obstacle in the achievement of high yields in this reaction. Earlier attempts saw a high degree of polymerization, discernible as a layer of sticky black substance on the sides and bottom of the reaction flask. Concentrations of CHD were then iteratively varied in order to achieve a better ratio of hydrogen donor to reactant, and the qualitative amounts of polymerized material were diminished. The fully cyclized blue-green bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin product **5** has been isolated from several reactions in moderate yields (15-30%), but has proved difficult to isolate in pure form, and therefore characterization has been incomplete. Recently, we have begun to vary the reaction conditions. Toluene has been substituted for chlorobenzene and CHD, acting as both solvent and hydrogen donor. Polymerization has still been an issue in this reaction, however. It is unclear at which step the polymerization is occurring, due to the radical nature of two of the intermediates. Though it could occur at either step, it is more likely that polymerization is occurring at the planar diradical species **10**. This is due to the close proximity of the adjacent *meso*-phenyl ring (approximately 3.1 Å, see

Figure 5 below) in **9**, which acts as a radical quencher. This radical transfer to the outside structure of the molecule is expected to be fast, whereas the hydrogen donation to **10** to form **11** is expected to occur more slowly, due to the intermolecular nature of this part of the reaction. At this point, the radical would have more time to react with other species in solution, presumably more molecules like itself, to form polymers and oligiomers. However, as stated above, it is unclear how exactly the polymers are forming; it is only known that they are in fact forming and that they have been a stumbling block in achieving high yields of the target compound, **5**.



Scheme 6. Proposed mechanism for formation of **5**.

A second product was also isolated from this thermal Bergman cyclization reaction: 2,3-diethynyl-5,20-diphenyl-piceno[10,11,12,13,14,15-fghij]porphyrin **6**. This product has been cyclized only on one side of the molecule, instead of on both sides as in the case of **5**. A crystal structure has been successfully obtained for this molecule (Figure 4), and shows several degrees of distortion (Figure 5). Without a crystal structure of compound **4** it cannot be told if this distortion is the cause of the incomplete cyclization of **6**. Reasons behind the formation of both products **5** and **6** are yet to be elucidated.



Atom A	Atom B	Dist (Å)
N2	N4	4.342
N1	N3	3.914
C49	C51	2.995
C50	C52	4.273
C42	C49	3.169
C44	C51	3.063
C12	C13	1.380
C12	C49	1.414
C49	C50	1.181
C13	C51	1.424
C51	C52	1.191

Figure 4. X-Ray structure and selected bond lengths of **6**.

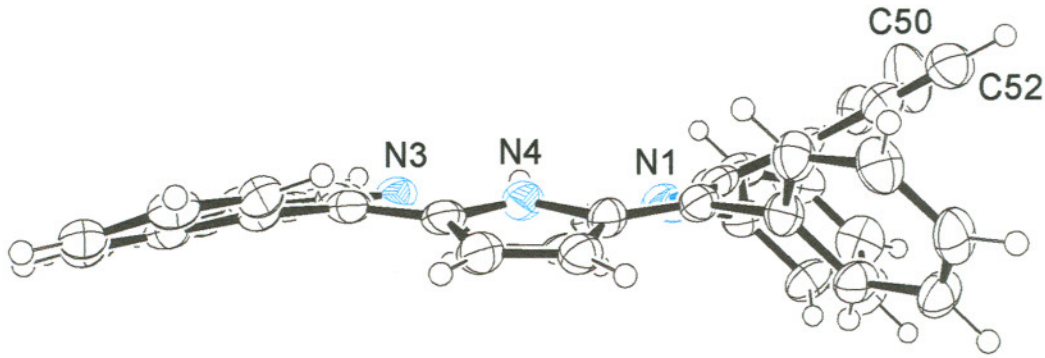


Figure 5. X-Ray structure of **6**, side view.

Experimental

Materials and General Procedures

All chemicals and solvents used were of the highest purity available from Aldrich and Strem. Air-sensitive reactions were carried out under nitrogen using Schlenk techniques and air-sensitive compounds were handled in an inert atmosphere dry box. Compounds were purified using flash chromatography with activated neutral aluminum oxide. ^{1}H and ^{13}C NMR were recorded on a VXR 400 or Gem 300 NMR spectrometer using the residual proton resonance of the solvent as an internal reference. Infrared spectra (KBr) were recorded on a Nicolet 510P FT IR spectrophotometer. Elemental analyses were obtained from Robertson Microlit Laboratories, Inc.

Synthesis of compounds

5,10,15,20-Tetraphenylporphyrin (1): Synthesized by following literature procedure. [12] Yield: 20%. ^{1}H NMR ($CDCl_3$): δ 7.756-7.804 (m, 12H, meso-ArH), 8.25 (dd, J = 1.6, 1.6 Hz, 8H, meso-ArH), 8.879 (s, 8H, β-pyrrolic H).

2,3,12,13-Tetrabromo-5,10,15,20-tetraphenylporphyrin (2): To a solution of **1** (500 mg, 0.814 mmol) in ethanol-free $CHCl_3$ (75 mL), N-bromosuccinimide (724 mg, 4.07 mmol) was added. The resulting solution was refluxed at 80 °C for 24 hours. The solvent was removed under reduced pressure and the resulting solid was purified by

recrystallization from CH_2Cl_2/MeOH to afford purple crystals. Yield: 80%. ^1H NMR ($CDCl_3$): δ 7.758-7.816 (m, 12H), 8.18 (dd, J = 1.5, 2.1 Hz, 8H), 8.70 (s, 4H).

2,3,12,13-Tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin (3): To $(Ph_3P)_4Pd$, a solution of **2** (500 mg, 0.538 mmol) in dry THF (30 mL) was added at room temperature. Then, trimethyl(trimethylstannanylethynyl)silane (842 mg, 3.23 mmol) in dry THF (15 mL) was added to reaction mixture and refluxed at 70-80 °C for 6 hours. The solvent was removed under reduced pressure and the resulting solid was purified by activated neutral aluminum oxide column chromatography using 40% CH_2Cl_2 in hexane. R_f in CH_2Cl_2: hexane (1:1) on neutral aluminum oxide TLC: 0.587. Yield: 90%. ^1H NMR ($CDCl_3$): δ 0.183 (m, 36H), 7.694-7.731 (m, 8H), 7.776-7.812 (m, 4H), 8.167 (d, J = 7.2 Hz, 8H), 8.634 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 1.011, 99.349, 109.672, 120.549, 127.395, 128.883, 129.422, 134.226, 135.760, 140.488, 141.604, 151.752. IR (cm^{-1}): 629.43, 657.29, 701.90, 756.68, 799.68, 853.37, 898.18, 1001.35, 1030.78, 1099.93, 1140.47, 1243.09, 1469.55, 1598.62, 2131.18, 2925.5, 3364.97. Anal. calcd. for $C_{64}H_{62}N_4Si_4$: C, 76.922; H, 6.259; N, 5.610. Found: C, 77.77; H, 7.53; N, 4.62.

Zinc (II) 2,3,12,13-tetrakis(trimethylsilylethynyl)-5,10,15,20-tetraphenylporphyrin (7): To a solution of **3** (500 mg, 0.501 mmol) in $CHCl_3$ (200mL), 1.2 equivalents of zinc acetate dihydrate (130 mg, 0.601 mmol) in MeOH (50mL) were added. The reaction mixture was stirred at room temperature for 1 hour to afford the green compound. The solvent was removed under reduced pressure and the resulting solid was purified by

silica gel column chromatography using 1:1 CH_2Cl_2: hexane. Yield: 95%. ^1H NMR ($CDCl_3$): δ 0.226 (s, 36H), 7.630-7.679 (m, 8H), 7.748-7.773 (m, 4H), 8.063 (d, J = 7.2 Hz, 8H), 8.591 (s, 4H).

2,3,12,13-Tetraethynyl-5,10,15,20-tetraphenylporphyrin (4): To a solution of **3** (200 mg, 0.200 mmol) in THF (40 mL), 1 M solution of tetra-butyl ammonium fluoride (262 mg, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was evaporated off and resulting residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The crude compound was purified by activated neural aluminum oxide column chromatography using CH_2Cl_2:hexane (1:1) as solvent. R_f in CH_2Cl_2: hexane (1:1) on neutral aluminum oxide TLC: 0.437. Yield: 90%. ^1H NMR ($CDCl_3$): δ 3.57 (s, 4H,), 7.654-7.703 (m, 8H), 7.776-7.826 (m, 4H), 8.08 (d, J = 8.1 Hz, 8H), 8.83 (s, 4H). IR (cm^{-1}): 607.73, 687.13, 699.29, 734.78, 768.13, 753.24, 801.04, 960.27, 1001.48, 1030.49, 1073.65, 1088.72, 1156.72, 1137.49, 1175.37, 1251.02, 1280.75, 1341.52, 1375.74, 1442.23, 1475.69, 1506.46, 1550.55, 1597.54, 1713.44, 1828.40, 1891.11, 2104.62, 3047.43, 3290.11. Anal. calcd. for $C_{52}H_{30}N_4 \cdot H_2O$: C, 85.684; H, 4.428; N, 7.691. Found: C, 85.44; H, 4.14; N, 7.25.

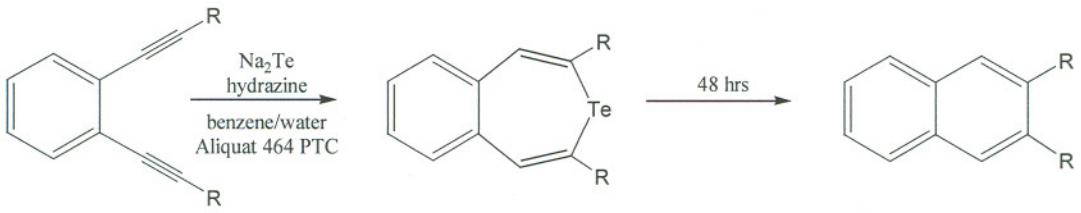
Zinc (II) 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin (8): To a solution of **7** (500 mg, 0.501 mmol) in THF (150 mL), 1 M solution of tetra-butyl ammonium fluoride (262 mg, 1.00 mmol) in THF (1 mL) was added. The reaction mixture was

stirred at room temperature for 2 hours. After completion of the reaction, the solvent was evaporated off and resulting residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude compound was purified by silica gel column chromatography. Yield: 55%. ^{1}H NMR ($CDCl_3$): δ 3.611 (s, 4H,), 7.616-7.670 (m, 8H), 7.760-7.784 (m, 4H), 8.033 (d, J = 6.9 Hz, 8H), 8.823 (s, 4H).

Thermal cyclization of 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin (4): To a solution of **4** (20 mg, 0.028 mmol) in benzene (15 mL), 1,4-cyclohexadiene (2.36 mL) was added. The reaction mixture was heated at 80 °C for 20 hours. The solvent was evaporated under reduced pressure and the resulting solid was purified by activated neutral aluminum oxide column chromatography using 2% ethyl acetate in CH_2Cl_2 to produce bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin **5** and 2,3-diethynyl-5,20-diphenyl-piceno[10,11,12,13,14,15-fghij]porphyrin **6** in 15% and 25% yields, respectively. The complete characterization of **5** is yet to be carried out, and further efforts are being made to obtain these products in good yield. Characterization data for **5**: MALDI-TOF MS m/z = 707 [M^+]. Characterization data for **6**: R_f in CH_2Cl_2: hexane (4:1) on neutral aluminum oxide TLC: 0.857. ^{1}H NMR ($CDCl_3$): δ 3.618 (s, 2H), 7.754 (dd, 2H), 7.75 (m, 6H), 7.784 (q, 4H), 8.156 (d, 4H), 8.491 (s, 2H), 8.59 (d, 2H), 8.74 (d, 2H), 9.36 (t, 4H).MALDI-TOF MS m/z = 708 [M^+].

Future Work

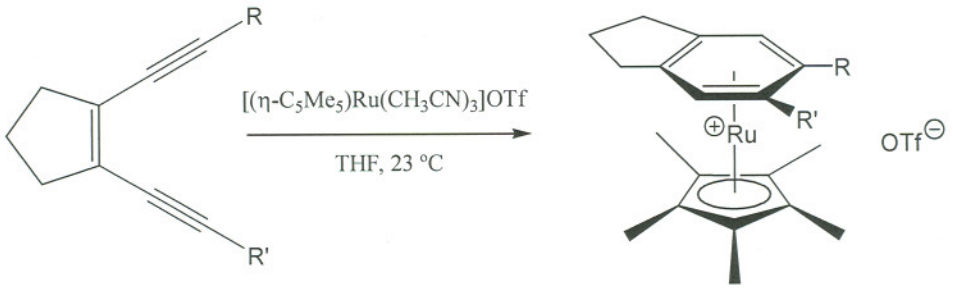
At the writing of this paper, work is about to begin to employ two new methods to cyclize **4**, both of which involve the use of a metal catalyst. A recent paper by Landis *et al* [17] describes the tellurium mediated cyclization of acyclic enediynes. In this method, sodium telluride is combined with hydrazine, and Aliquat 464 phase transfer catalyst (PTC) in a benzene/water mixture to form the cyclized product in 70% yield at 40 °C (Scheme 7). The exact mechanism for this reaction is not known, but it is believed to proceed by a radical-anion-chain mechanism, with hydrazine functioning as the electron donor. They reported no intramolecular polymerization reactions, but did experience problems with intermolecular polymerization of one species that had n-hexyl groups placed ortho to the alkynes. The tellurium-mediated cyclization in this molecule produced a mixture of compounds that were presumed to be products of hydrogen atom abstraction or cyclization with the vicinal alkyl groups. However, since these groups are absent in our molecule, we do not anticipate like problems in Te mediated cyclization of 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin (**4**).



Scheme 7. Te mediated cyclization of acyclic enediynes.

Another recent paper, by O'Connor *et al*, [18] described the use of tris(acetonitrile)cyclopentadienylruthenium (III) triflate as a catalyst for room

temperature cyclization of acyclic enediynes. In this reaction, the Ru complex drives the enediyne cyclization in THF at 23 °C, and affords cyclized product in 64-88% yield, depending on the R groups (Scheme 8). The detailed mechanism for this reaction has not been established, but it is believed that ruthenium forms a π complex with the alkynes, initiating the cyclization reaction. If this is indeed the mechanism, this may be problematic for use with **4**, since there are four phenyl rings on the periphery of the molecule with which the Ru complex may bind, instead of initiating the cyclization of the enediyne unit. In fact, in a previous paper, O'Connor *et al* [19] reported that the enediynes with a phenyl backbone did not readily undergo cyclization, due to interference of the aromatic system with Ru complex. This reaction instead produced a mixture of Ru bound starting material, and a small amount of the cyclized product. We plan to use this catalytic method, however, because it may cause the phenyl rings in **4** to become planar to the porphyrin core, thus forcing them closer to the enediyne moiety and facilitating cyclization.



Scheme 8. Ruthenium mediated cyclization of acyclic enediynes.

Conclusions

This paper has shown the work done thus far on synthesis of a molecule to be as an *in vivo* imaging agent. The goal is to synthesize a molecule containing a porphyrin chromophore and a near-IR emitting lanthanide center. Bergman cyclization has been

employed to create a porphyrin with an extended conjugated structure. Work is ongoing to cyclize zinc (II) 2,3,12,13-tetraethynyl-5,10,15,20-tetraphenylporphyrin, and to synthesize bis-piceno[20,1,2,3,4,5,10,11,12,13,14,15-fghij]porphyrin in good yield. Future work will include metal mediated cyclization of the free base complex, as well as insertion of lanthanides to assess the near-IR emitting capability of the molecule.

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